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RESEARCH PAPER

Will time heal? A long-term follow-up of severe disorders of consciousness

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Abstract

Objective: Little is known about the long-term outcome of patients with disorders of consciousness (DOCs) such as unresponsive wakefulness syndrome (UWS) or minimally conscious state (MCS). We describe the disease course of a large group of DOC patients 2–14 years after brain damage. **Methods**: In 102 patients (59 UWS, 43 MCS), clinical and demographic variables from disorder onset were related to the patients' outcomes 2–14 years after discharge. Etiology, age at event, time since onset, gender, and home care versus institutional care were assessed as predictors and similarities and differences between UWS and MCS determined. **Results**: Seventy-one percent of the patients had passed away or showed no improvement in condition. Twenty-nine percent regained consciousness and developed some communicative capacities. The time a syndrome persisted did not predict clinical outcome in either condition. Six patients regained consciousness after more than 3 years. Of these, five had been UWS (42% of recovered UWS, three traumatic origins, one tumor, one hypoxia) and one MCS (5% of recovered MCS, traumatic origin). In UWS, younger patients, those cared for at home, and in tendency those with traumatic origins, were more likely to recover. In MCS, no reliable outcome predictors were found. **Interpretation**: Current predictors are too vague for single patient predictions. This study identifies a subgroup of late-recovering patients, casting doubt on the 12-month boundary, after which UWS is stated to be permanent. Routine reexamination, use of more reliable outcome predictors and research determining optimal care settings are needed to inform the crucial decisions made for these patients.

Introduction

Fast emergency rescue and efficient intensive care have considerably improved the chance to survive severe brain damage. Unfortunately, physical survival is not always paralleled by mental recovery, and patients sometimes remain in states of disorders of consciousness (DOC)s such as the unresponsive wakefulness syndrome (UWS; formerly known as the vegetative state[1]) or the minimally conscious state (MCS).[2] UWS patients show no signs of awareness of themselves or their environment. Still, they open their eyes spontaneously and have sleep–wakefulness cycles.[3,4] MCS patients show inconsistent signs of awareness, but are usually able to fixate or to follow simple commands.

Both states can become permanent and for both there are very few indicators of functional outcome. The most common predictors are etiology, age, and time since injury. UWS patients appear more likely to recover, if they are under the age of 40 and following traumatic brain injury (TBI) than following other causes.[2–9] The few follow-up studies on MCS so far suggest a similar etiology–outcome relationship.[6,10] Regarding illness duration, the Multi Society Task Force (MSTF) on persistent vegetative state expects UWS to become permanent after 3 months following hypoxia and after 12 months following TBI.[3,4] For MCS, no such boundaries exist, but good recovery is likewise thought to begin within the first few months after onset.[5,7,11]

Accordingly, follow-up studies typically concentrate on the first 12 months after onset.[4,12,13] Consequently, the

proportion of deaths occurring within the first year might be inflated by decisions to terminate further treatment.[14] Without more data on long-term recovery chances, prognosis factors, and optimal care, crucial decisions might rely on incomplete information.

DOC patients often quickly leave the medical system. In the United States, they are placed "within weeks of their injuries in widely distributed homes and nursing homes [...]. Thus, they are underrepresented in rich longitudinal databases [...] and difficult to recruit"[15] (p. 1852). Therefore, a broad and detailed database on the natural course of patients with severe DOC is needed.

Lammi[10] examined 18 MCS patients 2–5 years after TBI. Avesani[16] conducted a 5-year follow-up on two UWS patients. Both studies indicate that recovery might be possible after more than 12 months. Estraneo[9] followed 50 UWS patients for up to 4 years (mean 2.08 years), identifying six patients (12%) with late recovery of consciousness. Recovery occurred more often in young TBI patients but even one hypoxia patient regained consciousness after more than 1 year. Nakase-Richardson[17] and Whyte[18] describe the 5-year outcome of 108 TBI patients and show that patients continue to improve for several years post injury. A similar optimistic result was shown by Nakase-Richardsen in a cohort of the 122 military personnel with DOC resulting from mostly military-related TBI.[19] However, they[17–19] report on patient groups who, according to current prognosis factors (TBI, young, recruited shortly after event) had the best recovery chances and results need not generalize to the much broader group of patients with severe DOCs from varying etiologies.

Several studies investigated sex differences in the rehabilitation of brain injuries in general, but not following DOC. Current studies report that women experience greater disabilities, have a higher mortality rate[20–22], and show poorer long-term readjustment than men.[23]

Furthermore, no study compared the outcomes of different types of care, such as patients being cared for at home versus in nursing homes. Patients treated at home are particularly understudied and it remains unclear if similar problems or recovery rates occur in different kinds of environments.[15]

Here, we investigate the long-term outcome of a large group of UWS and MCS patients with various etiologies and across a wide age range, 2–14 years (mean after 7.9 years) after treatment at a rehabilitation center. Follow-up considerably exceeds previously established boundaries. Time until recovery onset is assessed and possible long-term-outcome differences between the syndromes of UWS and MCS and the applicability of UWS-outcome predictors such as etiology, age at onset, or duration to MCS are examined. Long-term outcomes are compared between men and women and institutional versus home environments.

Methods

Participants

The initial sample consisted of 175 patients with DOCs treated between 1994 and 2005 at the neurorehabilitation hospital "Kliniken Schmieder" (Allensbach, Germany). Medical files documented patients to have been in either a UWS ($n = 92$) or a MCS ($n = 83$). File ascertainment ensured the original diagnoses. Evaluated were daily-recorded nursing and therapy protocols and scores on the German Koma Remission Skala (KRS – coma remission scale[24]), conducted every 4 weeks by the physician in charge. A patient was defined to be in UWS if all available data conformed to the MSTF definition of UWS.[3,4] If a patient showed signs of awareness but was not able to functionally communicate or use at least two objects correctly, he was assigned to the MCS group.[2]

Materials

The German "Koma remission scale"

Cognitive functioning was evaluated using the KRS.[24] The KRS is a scale designed to monitor and protocol the improvements of coma, UWS and MCS patients in early rehabilitation. The KRS has good psychometric properties and its use is recommended in Germany.[24] It was routinely used at the Kliniken Schmieder and all patients had multiple documented KRS scores. For comparability, the KRS was also used for follow-up testing. A translation of the KRS is provided as Table S4.

Glasgow outcome scale

The Glasgow outcome scale (GOS)[25] was used to assess patients' progress at follow-up according to five outcome categories:

1 Death
2 Vegetative state
3 Severe disability
4 Moderate disability
5 Good recovery

Patients deceased at follow-up were classified as GOS 1. At follow-up, patients were classified as GOS 2 if they were either in UWS or in MCS. UWS, and MCS were not further differentiated, since follow-up data were initially obtained from caregivers and correctly distinguishing MCS from UWS is a challenge even for trained professionals.[26,27] Patients are referred to as recovered (GOS 3

or better), if they were able to functionally communicate (one of the upper boundaries of MCS). Functional communication is such a milestone for relatives that it will not be missed or forgotten and could be reported reliably (see also[28]). Additionally, we visited a group of 30 UWS and MCS patients for reexamination. Our results on KRS and GOS did not differ from those given by relatives.

Procedure

A structured telephone interview was conducted 2–14 years after the initial event. Successfully interviewed were 92 (59 former UWS and 43 former MCS), out of the original 175 patients. The patients, their relatives, or caregivers, were asked to complete the KRS for comparison with clinical data. If the patients were already deceased, the relatives were interviewed about the patients' last cognitive and medical state, using the same questionnaire. Thirty former patients were individually reexamined and comparisons between the relatives' and the medical staff's KRS–scores turned out to be mostly identical, varying maximally by ± 1 point. Therefore, distortion of patients' abilities by caregivers seems highly unlikely.

Additional questions were asked, depending on the patients' condition (when/why did death/recovery occur) and life circumstances (at home or in an institution). Age, date of event, duration of stay in the rehabilitation unit, initial KRS scores, and etiology were taken from clinic files.

Statistics

Because some data violated sphericity and normal distribution, nonparametric statistics were used. Significance level was set at $P = 0.05$. Multiple comparisons were adjusted for using the Bonferroni correction.

To compare UWS and MCS patients at different time points, we used Friedman's nonparametric two-way analysis of variance (ANOVA) for dependent samples. Dunn's post test was used to compare differences in sum of ranks between two variables. The Mann–Whitney *U* test was used as a nonparametric alternative to the *t*-test.

The relationship between etiology, gender, type of care, and a patient's outcome was assessed using Fisher's exact test, calculating likelihood ratio of clinical improvement, sensitivity, and specificity. For contingency tables with more than two rows or columns, chi-square calculations for large contingency tables were used, assessing nonrandom association between rows and columns.

To examine the influence of age on a subsequent death or improvement, the point-biserial correlation was calculated.

Results

Demographic description of the followed up patients

Table 1 summarizes the groups' demographic and clinical characteristics. For detailed information on single patient data see Table S1 (MCS patients) and Table S2 (UWS patients).

KRS

Figure 1 illustrates patients' KRS scores. For UWS patients, differences between assessments were highly

Table 1. Patient characteristics and outcome data.

	MCS (n = 43; M [SD])	UWS (n = 59; M [SD])
Age	45.1 years (17.1 years)	44.2 years (14.8 years)
Duration of stay at the rehabilitation unit	119.4 days (82.6 days)	105.6 days (115.9 days)
Time between event and admission (where the first KRS was conducted)	1.9 months (1.6 months)	7.9 (11.4)
Time until Follow-up	8.0 years (3.5 years)	8.8 years (3.1 years)
Patients deceased at follow-up (GOS 1)	15 (35%)	28 (48%)
Patients with no change in condition (GOS 2)	10 (23%)	19 (32%)
Patients recovered (all patients able to functionally communicate; GOS 3–5)	18 (42%)	12 (20%)
GOS 3	10 (23%)	11 (18%)
GOS 4	5 (12%)	1 (2%)
GOS 5	3 (7%)	0 (0%)
Gender distribution (m/f)	27/16	48/11
Type of injury (TBI/Hypoxia/Others)	24/6/13	25/19/15

MCS, minimal consciousness state; UWS, vegetative state; M, arithmetic mean; SD, standard deviation; GOS, Glasgow outcome scale; m, male; f, female; TBI, traumatic brain injury. Patients were considered as recovered if they at least reached the ability to functionally communicate again. Type of injury, Others = combined causes of condition (TBI and Hypoxia) as well as tumors, stroke or encephalitis. None of these parameters (except of "time between event and admission") differed significantly between the two patient groups.

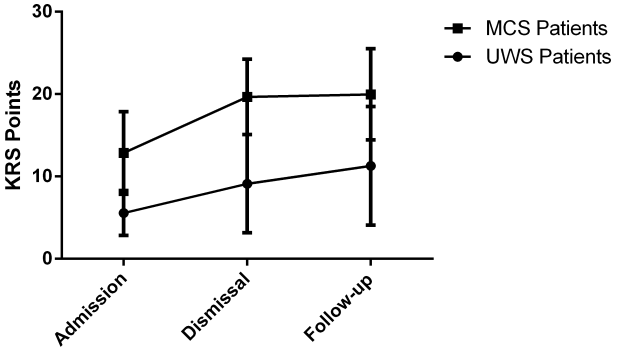

Figure 1. KRS scores of UWS and MCS patients across the three time points of admission, discharge, and follow-up on the group level. Vertical bars are standard deviations.

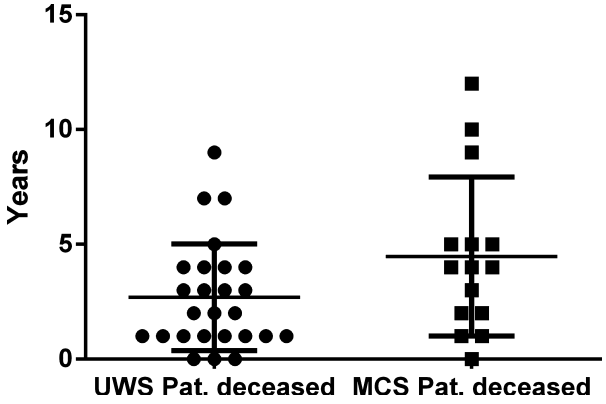

Figure 2. Life expectancy of UWS and MCS patients in this study. Vertical bars are means and standard deviations.

significant (Fr(2) = 56.82; $P < 0.0001$,). They had higher KRS scores at discharge than at admission (difference-in-rank-sum = −49.50, $P < 0.001$,), and at follow-up compared with admission (difference-in-rank-sum = −67.50, $P < 0.001$). The difference between discharge and follow-up did not reach significance (difference-in-rank-sum = −18, $P > 0.05$).

Likewise, in MCS patients the difference between assessments was highly significant (Fr(2) = 42, $P < 0.0001$). Significant differences between admission and discharge (difference-in-rank-sum = −38.0, $P < 0.001$), as well as between admission and follow-up (difference-in-rank-sum = −46.0, $P < 0.001$) were also present, but there was, on average, no significant change between discharge and follow-up (difference-in-rank-sum = −8.0, $P > 0.05$).

Life expectancy and the impact of etiology, age, gender, and type of care on subsequent death

Life expectancy

UWS patients who had died did so on average 2.7 years (SD 2.3, range 0–9 years), MCS patients, on average, 4.5 years after discharge (SD 3.4, range 0–12 years). Because of the wider range in MCS, (see Fig. 2), this difference was only marginally significant (Mann–Whitney *U* test = 128.5, $P = 0.069$). However, MCS patients clearly tended to have a longer life expectancy. The most common cause of death in both patients groups was pneumonia. Other common reasons were multiple organ failure, infection, stroke, and embolism.

Age

Figure 3 shows patients' age at event, their condition at the beginning of the rehabilitation, and whether or not they were still alive at follow-up. There was no clear correlation between a patients age at event and a subsequent death (UWS patients: $r = -0.173$, $P = 0.189$; MCS patients: $r = -0.265$, $P = 0.086$).

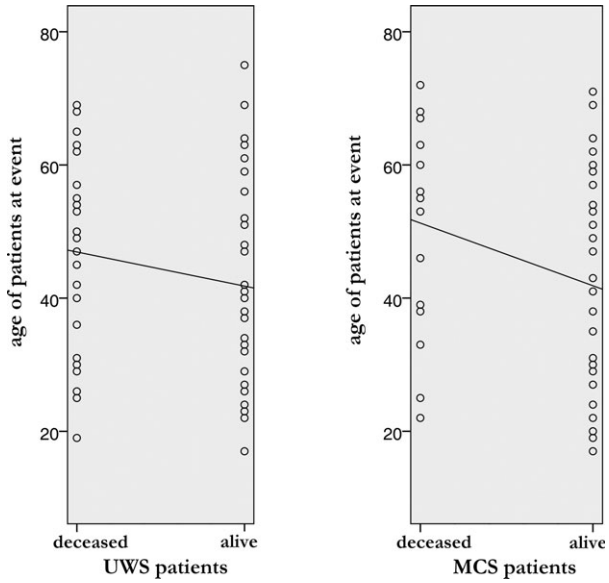

Figure 3. UWS and MCS patients alive and deceased at follow-up depending on the patient's age at event.

Etiology

No meaningful relationship between etiology (TBI, hypoxia, others) and subsequent death was identified. Chi-square contingency tables were insignificant for UWS ($\chi^2(2) = 2.28$, $P = 0.245$) and MCS ($\chi^2(2) = 1.08$, $P = 0.583$) patients.

Fisher's exact test showed no differences between the likelihood of death in UWS or MCS following TBI ($P = 0.24$), anoxic causes ($P = 1.00$), or other etiologies ($P = 0.71$).

Gender

In both disorders, male and female patients were equally likely to die. UWS: ($P = 0.530$, sensitivity = 0.15, specificity = 0.78, Likelihood ratio = 0.68); MCS: ($P = 0.34$, sensitivity = 0.27, specificity = 0.57, Likelihood ratio = 0.62).

Type of care

UWS patients tended to die more often in institutional care ($P = 0.051$, sensitivity = 0.29, specificity = 0.41, Likelihood ratio = 0.48). From 34 patients cared for institutionally, 20 passed away, whereas from 21 patients treated at home, 15 were still alive.

In MCS, no association between a subsequent death and type of care was identified ($P = 0.26$, sensitivity = 0.28, specificity = 0.50, Likelihood ratio = 0.56).

Time course of recovery

Twelve UWS patients recovered consciousness over time (GOS 3 and better). Seven of them (58%) did so within the first few months after the causal event. The other five (42%) began to recover after 3–5 years. On average, consciousness was recovered 22.4 months after the event (range 1–60 months).

Eighteen MCS patients recovered consciousness. Sixteen (89%) showed a gradual improvement from acute coma to UWS and MCS immediately after the event and into the range of severe disability within the first 3 months. However, two patients (11%) improved after 10 months or 3 years, respectively. On average, MCS patients recovered 4.0 months after the event (range from 1–36 months).

The mean recovery time differed between UWS and MCS patients (Mann–Whitney U test = 28.00, $P = 0.0006$), UWS patients recovering later. Patients that recovered consciousness after more than 12 months are described in more detail in Table S3.

Impact on recovery of etiology, age, gender and type of care

Etiology

In UWS, recovery was somewhat more likely following TBI than hypoxia ($P = 0.056$; sensitivity = 0.32; specificity = 0.95; Likelihood-ratio 6.08). Following TBI, patients were six times more likely to recover to GOS 3 or better. Taking the rare "other" origins (encephalitis, tumors, electric shock) also into account, only a slight trend was found ($\chi^2(2) = 4.74$, $P = 0.09$) due to the large variability among other causes.

MCS etiology did not affect prognosis at all. The distributions were similar for traumatic and hypoxic origin ($P = 1.00$; sensitivity = 0.46; specificity = 0.50; Likelihood-ratio = 0.92) and also taking other etiologies into account ($\chi^2(2) = 0.84$, $P = 0.66$). Thus, all etiologies had similar chances to improve from MCS.

Age

In UWS, but not MCS, younger age was correlated with subsequent recovery (UWS: $r = -0.309$; $P = 0.017$; MCS: $r = -0.235$; $P = 0.129$).

Gender

Gender had no influence on subsequent recovery in either group (MCS: $P = 1$, sensitivity = 0.39, specificity = 0.64, Likelihood-ratio 1.08; UWS: $P = 1$, sensitivity = 0.15, specificity = 0.80, Likelihood-ratio = 0.79).

Type of care

In the UWS group there was a significant relationship ($P = 0.02$, sensitivity = 0.43, specificity = 0.88, Likelihood ratio = 3.6). Nine of the 13 recovered patients were cared for at home. On the other hand, 30 of 42 patients without progress were cared for in an institution. In MCS, type of care was not associated with outcome ($P = 0.14$, sensitivity = 0.62, specificity = 0.70, Likelihood ratio = 2.1).

Treatment onset

There was no significant correlation between months before admission to rehabilitation and recovery for either UWS ($r = 0.07$, $P = 0.62$) or MCS ($r = -0.13$, $P = 0.44$).

Discussion

We investigated the disease course of UWS and MCS patients from various etiologies 2–14 years after disease onset. Very few studies have assessed the long-term outcome of similarly sized groups of DOC patients[17–19] and those who did, did not distinguish between UWS and MCS.

In general, MCS patients were more likely to survive than UWS patients; on average they lived longer (albeit sometimes without further progress) and regained

consciousness more often and significantly faster. They also had better chances to recover to a higher outcome level, confirming MCS as a less severe disorder than UWS. The better outcome of MCS patients cannot be accounted for solely by different starting points. UWS patients arrived at the rehabilitation center on average after 1.9 months (SD = 1.6), whereas MCS patients were admitted after 7.9 months (SD = 11.4). Thus, the UWS patients had every chance to recover. By contrast, patients in MCS had been in this condition for quite a while, such that further progress was by no means guaranteed. Still they improved more often and to a better outcome than UWS patients did.

For UWS, this study confirms previous results, with younger patients and in tendency also TBI patients having better chances to recover.[3,4,29] These factors were significant on a group level, but their magnitude comes nowhere close to allowing for single case prediction. Etiology may have lost some of its prognostic power due to medical progress. For instance, therapeutic hypothermia selectively improves outcome of hypoxic coma patients and significantly reduces the mortality rate and severity of persisting deficits following cardiopulmonary reanimation.[30] Hypothermia has risen to a standard treatment in intensive care units relatively recently,[31] potentially reducing the previous advantage of TBI over other causes. A similar case might be made for age: Better general health at higher ages and advances in medical care may have reduced the younger patients' advantage.

For MCS, we failed to find any prognostic factors: Neither age, nor illness duration, or etiology had any significant impact on prognosis. MCS not only differs from UWS in presentation but also in course and outcome deserving specific clinical and scientific attention. The clinical distinction between UWS, MCS or other states such as looked-in syndrome, can be problematic and a misdiagnosis rate of up to 40% is assumed.[26,27,32,33] We made every effort to confirm the patients' initial diagnoses[28] and the continuing difference in KRS scores indicates successful group separation. Following an initial misdiagnosis rate of up to 40%, there would be no basis for stable differences.

Investigating recovery onset, two groups of patients were identified: one that began to recover early and a second group, beginning to recover 3–5 years after the event. In UWS, this second group is hardly smaller than the group recovering within the first 12 months. Therefore, on an individual patient level, the statement that UWS becomes permanent after 1 year is not confirmed. This study identifies UWS patients who recover even after more than 4 years, very late recovery occurring in one TBI patient, one tumor patient and one hypoxia patient.

The majority of MCS patients recovered within the first few months. But even in MCS, late recovery was observed in two patients, which is in line with Lammi et al. who concluded: "prognostic statements based on length of time a person is in the MCS cannot be made with confidence"[10] (p. 746). Therefore, setting a time limit on recovery expectations, with all the known consequences like restriction of further therapies and dismissal from rehabilitative hospitals, appears premature.

For both patient groups significant advances could be achieved during rehabilitation, even if patients received treatment after many months. For example, a MCS patient (Table S1, patient 5) who was admitted to the rehabilitation center 4.5 years after hypoxia with a KRS score of 14 improved to a KRS score of 24 as therapists were able to establish a communication channel. Although she remained completely dependent in everyday life, she became able to communicate her needs and feelings. Beneficial effects of active rehabilitation of DOC are in line with Nakase-Richardson and Whyte, who also observe "a large number of cases of recovery of consciousness during the inpatient rehabilitation [...]" ([17] p. 63). Still, most patients, even if they regain communicative capabilities, remain disabled to varying, often considerable extents (see Tables S1, S2).

If progress is absent from the beginning, patients have a severely reduced life expectancy. This is not surprising, given their immobility and often impaired reflexes, putting them at risk for medical crises. More severe brain injuries might be expected to result in higher risk of death. Indeed, more UWS (48%) than MCS (35%) patients had passed away at follow-up and MCS patients lived longer even without further recovery (UWS about 2 years, MCS about 4 years). These data are in accord with general findings of higher life expectancy after TBI if mobility is regained.[34,35]

Gender had no influence on recovery in either patient group. Male patients and female patients did not differ in recovery chances or subsequent death rates. However, their genders were not equally represented in our sample.

Interestingly, in UWS type of care affected outcome. Nine of the 13 recovered patients were looked after at home, whereas 30 of the 42 who did not recover were cared for in an institution. UWS patients also tended to die more often if transferred into an institution after rehabilitative treatment. This may be due to factors such as familiar routines, a possibly enriched home environment, or closer contact between family members and patients, which may help prevent medical crises. On the other hand, motivational factors may influence the decision to take a patient home or more instable patients may be more likely to be transferred into institutional care. Our data is not detailed enough to identify specific factors influencing outcome or to differentiate between homes for the elderly and specialized facilities. Apparently

the type of care is statistically related to long-term outcome, but causes remain speculative.

In summary, this study has the following key findings: First, none of the routinely used prognosis factors for UWS showed any prognostic value for MCS. Second, even if prognosis factors were significant on a group level, effects were relatively weak and could not predict a single patient's outcome. More specific prognostic instruments, such as EEG markers[13,28,36–38] might facilitate better outcome prediction. Third, and most importantly, UWS and MCS do not become permanent after 1 year. There are patients with various etiologies recovering after several years in stable UWS or MCS. Finally, the care setting was related to the likelihood of recovery and with appropriate therapy even more patients might regain consciousness after being in UWS and MCS for several years. Thus, patients should have access to reexamination and optimal care including rehabilitative therapies even if the success of these therapies cannot be seen immediately.

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Authors´ Contribution

I. S.: acquisition, analysis and interpretation of data, drafting the manuscript. M. K.: acquisition of data, revision of the manuscript. J. K.: conception and design, interpretation of data, drafting the manuscript.

Conflict of Interest

None declared.

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Supporting Information

Additional Supporting Information may be found in the online version of this article:

Table S1. Individual data of MCS patients, this table includes individual data for each patient (gender, age at event, event year, year of death, etiology, coma remission scale scores at admission, discharge, and follow-up, Glasgow outcome scale scores a patients abilities of daily living, years of education, and where he is currently looked after).

Table S2. Individual data of UWS patients, this table includes individual data for each patient (gender, age at event, event year, year of death, etiology, coma remission scale scores at admission, discharge, and follow-up, Glasgow outcome scale scores a patients abilities of daily living, years of education, and where he is currently looked after)

Table S3. Description of patients with late recovery; this table includes individual data of all patients that begin to recover more than 12 months after the initial event.

Table S4. Translation of the KRS Scale.

